Original article

The association between metformin treatment and COVID-19 outcomes according to metformin continuation during hospitalisation

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Along with antidiabetic effects, metformin has anti-infective and anti-inflammatory properties [1]. We [2] and others [3] have showed that metformin treatment is associated with better outcomes in diabetic patients hospitalised for coronavirus disease 2019 (COVID-19). However, it is not known whether this beneficial association is due to metformin treatment prior to hospital admission, its continuation during the hospital stay, or both. Here, we assessed differences in outcomes for patients who continued to take metformin in hospital versus those who did not. We also studied the correlations between blood levels of metformin and common inflammatory markers.

The study population and methods have been described elsewhere [4]. Briefly, we collected data on consecutive diabetic patients admitted to Amiens University Hospital (Amiens, France) with PCR-confirmed COVID-19 between the start of the outbreak in France and May 23rd, 2020 (n = 145). We recorded each patient's baseline characteristics, medications, laboratory results, and COVID-19 outcomes. Medical and prescription records were screened for metformin prescription / administration during the hospital stay. Plasma and erythrocyte metformin levels were analysed in a subset of the patients (n = 25), according to a previously described method [5]. All the patients were followed up until discharge or death.

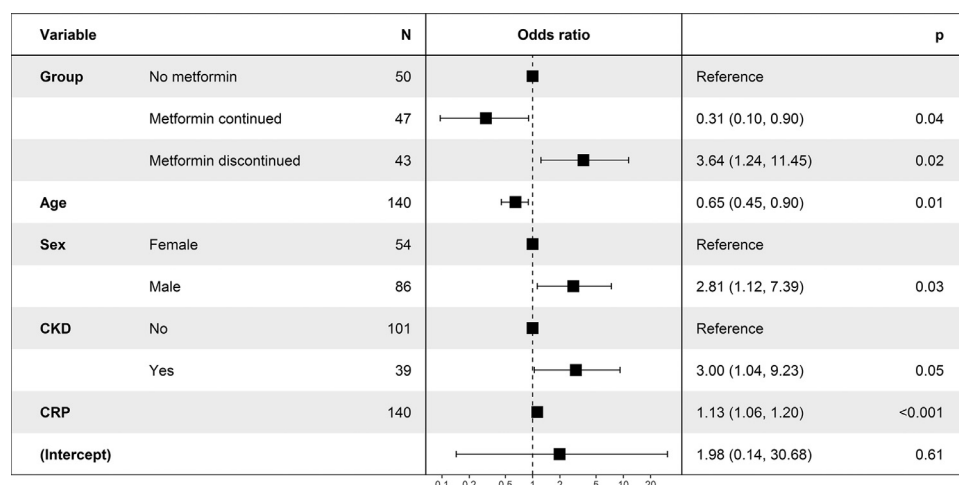Patients were categorised into "continuation of metformin throughout the hospital stay", "discontinuation of metformin on admission", and "no metformin" groups. Between-group comparisons were performed with the Mann–Whitney–Wilcoxon test (for two groups) or the Kruskal–Wallis test (for more than two groups) for numerical variables and Fisher's exact test for categorical variables. The association between these groups and the primary endpoint (a composite of intensive care unit admission or death) was probed in a logistic regression analysis. The secondary endpoints were the components of the primary endpoint, the need for mechanical ventilation and a composite of invasive mechanical ventilation or death. Correlations between metformin levels on one hand and the C-reactive protein (CRP) level, white blood cell count and lymphocyte count on the other hand were assessed using Spearman's correlation test.

The study complied with good clinical practice and the French legislation on clinical research and data protection. It was approved by the local institutional review board (IRB) and registered with the French National Data Protection Commission (reference: PI2020_843_0051). Patients who opposed data collection were excluded.

The three groups did not differ in their demographic characteristics and concomitant diseases, except that the prevalence of cardiovascular disease and chronic kidney disease was higher in the "no metformin" group (Table S1; see supplementary material associated with this article on line). With regard to laboratory data on admission (Table S2; see supplementary material associated with this article on line), the blood glucose level, CRP level and white blood cell count were highest in the "discontinuation group". Patients in the "continuation group" had the highest estimated glomerular filtration rate

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Variable		N	Odds ratio		p
Group	No metformin	50		Reference	
	Metformin continued	47		0.31 (0.10, 0.90)	0.04
	Metformin discontinued	43		3.64 (1.24, 11.45)	0.02
Age		140		0.65 (0.45, 0.90)	0.01
Sex	Female	54		Reference	
	Male	86		2.81 (1.12, 7.39)	0.03
CKD	No	101		Reference	
	Yes	39		3.00 (1.04, 9.23)	0.05
CRP		140		1.13 (1.06, 1.20)	<0.001
(Intercept)				1.98 (0.14, 30.68)	0.61

0.1 0.2 0.5 1 2 5 10 20

Fig. 1. Factors significantly associated with the composite endpoint (death or ICU admission) in a multivariable logistic regression analysis. Metformin treatment (none, continued, discontinued); age (per 10 years); sex (female vs. male); chronic kidney disease (CKD) (no, yes); and serum C-reactive protein (CRP) on admission (per 10 mg/L). The results were quoted as the odds ratio [95% confidence interval].

(eGFR) and the lowest CRP level. Patients in the "no metformin group" had the lowest blood glucose levels and eGFRs.

During the hospital stay (median [interquartile range] length: 12 [8 −23] days), the primary endpoint was met by 19.1% of the continuation group, 72.3% of the discontinuation group, and 43.1% of the no metformin group (Table S3 see supplementary material associated with this article on line). In a parsimonious multivariable analysis, the association between metformin continuation and a favourable outcome remained significant after adjustment for age, sex, concomitant disease (chronic kidney failure) and the CRP level (Fig. 1). The "other concomitant disease" (i.e. cardiovascular disease) variable and laboratory data (the blood glucose level, the white blood cell count, and the alanine aminotransferase level) were not retained in the final parsimonious model because they were not significant in the multivariable model.

There were no correlations between metformin levels and inflammatory marker levels.

It is possible to conclude (albeit with great caution, given the relatively small number of patients) that *i*) the beneficial association between COVID-19 outcomes and metformin treatment might be related to the drug's continuation during the hospital stay, rather than previous exposure; *ii*) the benefit associated with this continuation appears to be strikingly large; and, *iii*) this benefit does not seem to be related to metformin's anti-inflammatory properties because blood levels of metformin were not associated with the inflammatory marker levels (although again, the sample size was small). The putative mechanisms underlying metformin's protective effects in COVID-19 patients might include its well-known actions on the microvasculature [3] and cell death [6], in addition to the drug's actions on infection and inflammation [7]. It should be acknowledged that the clinical situation of the patients in the discontinuation group was worse than that of the patients in the continuation group (higher blood glucose level, CRP level and white blood cell count). Residual confounding cannot therefore be excluded, even after adjustment for the most important variables. A fourth group of patients with no prior metformin who received metformin during the hospital stay would have been of great value for our study. Unfortunately, this group was not available.

It is therefore clear that larger studies are needed to appraise more precisely the clinical value of continuing metformin treatment during a hospital stay (particularly in fragile patients) and to better

understand the mechanisms of metformin's actions on severe acute respiratory syndrome coronavirus 2 infections.

Appendix supplementary material

Supplementary materials (Tables S1-S2-S3) associated with this article can be found at http://www.scincedirect.com at doi . . .

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2021.101297.

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